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Bronchogenic Carcinoma

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In this paper, presented at a meeting of the A.O.A. Honour Society, Mr. Erickson discusses the etiology, diagnosis, pathology, spread, and treatment of one of Medicine's most vital problems. Emphasis is placed on the need for and the means of early detection.

WITHIN a period of a few decades bronchogenic carcinoma has risen from a position of relative rarity to one of the commonest malignancies.

In the British Isles the number of deaths from cancer of the respiratory tract has increased 120% during the same period in which all deaths from cancer increased only 22%. According to the reports of the Metropolitan Insurance Company the death rate bears a similar relationship in the U.S.A. It is reported that if the present trends on death rate of carcinoma of lung continue it may be estimated that the annual number of deaths from this disease in the U.S.A. will be 50,000 within the next few decades.

It is predominately a disease of males, the ratio of males to females being approximately 5 : 1, but this ratio has been decreasing over the years. The highest incidence is seen in the age group 40 to 60 years.

Etiology

1. *Heredity*—This has been shown to be a factor in breast cancer in certain strains of mice. Some investigators feel that it also has a relationship to primary lung carcinoma. Different racial predispositions have been shown by Burns and Kenning in a study in Detroit, in that Negroes seem to be less susceptible than whites. Steiner found that Mexican women exhibit a higher incidence than would be expected from general population figures.

2. *Chronic Pulmonary Irritants*

A. Inflammation

(1) *TB*—Most observers feel that when TB and bronchogenic carcinoma exist together in the same lung it is strictly coincidental.

(2) *Influenza*—This disease has been reported as a possible cause of lung cancer. However, Kelley and Dungal have found that the inhabitants of Iceland are relatively free of bronchogenic carcinoma in spite of some severe epidemics of influenza.

B. Chemical Irritants

(1) *Silica*—There has been no experimental proof that inhalation of silica bears any relationship to carcinoma of the lung.

(2) *Pneumoconiosis*—Kennaway has shown in a survey of coal miners in England that there is a lower incidence of carcinoma of the lung in this occupation. This would seem to rule out pneumoconiosis as a definite cause.

(3) *Pollution of Air*—Cancer of the lung has been thought for many years to be a disease of town folk, and whenever it has been possible to break down mortality rates for urban and rural areas it has been consistently higher in urban centres.

To some extent the greater incidence may be due to occupational risks and exposures in the arsenic, asbestos, chromate and nickel industries. Of more importance, according to Kennaway and Doll, is the increased incidence among gas workers, but this does not explain the overall urban increase. It has been postulated that the cause may be pollution of air with industrial and domestic smoke.

Three types of carcinogens of proven potency are known to be present in atmospheric dust: i—arsenic, ii—benzypyrene, iii—radioactive products. According to Kennaway it appears that benzypyrene is derived mainly from domestic chimney smoke, but arsenic is a component of industrial smoke.

(4) *Smoking*—The idea that smoking is an etiological factor in the production of bronchogenic carcinoma is not a new one. It was suggested that this was the reason for the increased incidence of the disease in cigar factory workers as far back as 1898.

According to the work of Doll and Hill on a survey of 2475 patients in London Hospitals it was concluded that smoking was a very important factor in the production of lung cancer, and that cigarettes seemed to be more to blame than pipes. The relative proportion of 5 : 1 male to female deaths from bronchogenic carcinoma has been attributed not to any sex differences in susceptibility, but to a greater use of tobacco by the male population.

There have been many theories put forth to explain the action of smoke as a carcinogen. Arkin and Wagner in 1936 postulated that the smoke caused an irritation and metaplasia of bronchiole epithelium and subsequent carcinoma. Tar, nicotine and arsenic are all components of tobacco and consequently have been thought to be the carcinogenic agents of cigarette smoke.

Lorenz reported that a certain strain of mice which were susceptible to lung cancer, when exposed to tobacco smoke for a maximum of 693 hours showed no increase in the number of tumours. Essenberg felt that perhaps they were not exposed sufficiently to this smoke and, upon repeating the experiment, was able to produce an increase in the number of lung cancers in these mice.

It has been said that statistics cannot prove causation but can only point out the probability of cause and effect. We are bound to take

what preventive measures we can, and accept the theory as though proof were absolute until further research leads to some modifications. It would seem that such a position has been reached with lung carcinoma, in that tobacco has been incriminated as the vehicle conveying an agent responsible for a large proportion of cases.

Diagnosis

Some contend that there are no symptoms or signs that will aid the clinician to recognize early bronchogenic carcinoma. Others confess a lack of specificity. All are agreed that there is a silent phase of variable duration during which the growth causes no symptoms, and that some produce symptoms too late to permit early detection.

In one survey it was quoted that an average of 10.5 months elapsed between the onset of symptoms and the establishment of a correct diagnosis, the delay attributed to the patient being 4.1 months, and to the physician 6.4 months. The failure of the physician to recognize or suspect the presence of primary pulmonary neoplasm early most commonly resulted from three errors:

1. a lack of awareness that minor respiratory symptoms, particularly in males in the 4-5-6th decades of life, often signal the clinical onset of carcinoma. This led to the second error.

2. failure to obtain a chest X-ray early in the disease.

3. significant departures from normal which were either overlooked or misinterpreted.

In order of their decreasing frequency the following are the symptoms first complained of by the patient:

1. Cough
2. Chest Pain
3. Dyspnea
4. Fatigue
5. Hemoptysis
6. Flu and Colds
7. Upper Extremity Pain
8. Weight Loss
9. Neck Swelling
10. Pneumonia
11. Back Pain
12. Chills and Fever

It is of interest to note that in a survey of 1205 cases studied by Ariel et al, it was found that hemoptysis represented only 5.6% of the total group's first symptom, although it was the most frequent symptom bringing the patient to the doctor. Because of the wide variation in symptoms and the rapidly fatal course of the disease the slightest clinical suspicion of carcinoma should be followed immediately by other diagnostic aids, which include:

1. Radiography
2. Bronchoscopy
3. Cytological Examination of bronchiole secretion
4. Aspiration Biopsy
5. Exploratory Thoracotomy.

Radiography

I. *Early Clinical and X-Ray features of Carcinoma arising in Main Stem Bronchi*

Figures show that from 60-80% of primary lung malignancies arise in this location. Characteristically they produce symptoms of bronchial irritation, infection or haemorrhage relatively early in their course. The most common early X-ray finding is a small unilateral, easily overlooked nodular enlargement of the hilar shadow.

Occasionally the endobronchial extension of the growth is large enough to produce signs of bronchial obstruction manifested by local wheeze or emphysema. More often the endobronchial portion is small at the onset, and therefore obstruction of a lobar bronchus resulting in X-ray evidence of atelectasis usually portends a well advanced malignancy. Arising close to the hilus, they are prone to invade vital mediastinal structures and adjacent lymph glands early. Very occasionally it has been found that squamous cell carcinoma growing very slowly remained localized for a considerable period of time, and curative excision usually depended upon diagnosis in the asymptomatic phase or during a period of minimal symptoms.

The most frequently encountered minimal symptoms of major bronchial tumours are cough and respiratory infections. Unfortunately cough has become such a common symptom among cigarette smokers that its diagnostic significance has been seriously compromised.

Approximately 1/3 of lobar carcinomas have a clinical onset characterized by recurrent respiratory infections. Their symptoms can best be described by the variety of diagnoses that have been made. The erroneous diagnosis tends to be confirmed by the prompt symptomatic improvement that results when antibiotics are employed. These patients frequently have cough and respiratory infection recur upon cessation of antibiotic treatment. It is a prime requisite that all pneumonic infiltrations be observed by X-ray until cleared if error is to be avoided — particularly in males in the age group 40-60.

It has been reported that up to 25% of lung abscesses have their origin in bronchogenic carcinoma. Therefore acute abscesses should also be watched closely in the light of these findings.

II. *Early Clinical and X-Ray features of Carcinoma arising in Segmental Bronchi*

This is the site of origin of 20% of primary lung cancer. Since these tumours arise in comparatively small bronchioles they are characterized by rather early atelectasis and infection of the distal pulmonary segment.

Chest X-rays are recognized easily as abnormal, but there is usually nothing to distinguish them from TB or pneumonia. With employment

of antibiotics the symptoms usually improve and partial clearing results. Pneumonitis that tends to recur in the same segment should strongly suggest bronchogenic carcinoma.

III. *Early Clinical and X-Ray features of Carcinoma in the Periphery*

These sites of appearance make up 5-20% of bronchogenic carcinoma and usually the lesions appear in X-ray as solitary masses, sharply circumscribed, and have been referred to as coin lesions. They frequently attain a large size before producing any symptoms. Symptoms eventually develop from extension of the growth to larger bronchi, if deeply placed, or if subpleurally situated, extension is to the pleura, thoracic cage, adjacent viscera and vertebral bodies, and this is usually associated with pain.

The Pancoast Tumour Syndrome symbolizes the hopelessly advanced form of a peripheral tumour arising above the superior sulcus. The early diagnosis of peripheral tumours generally depends on their detection by means of survey chest X-rays prior to symptoms, although an accurate diagnosis may have to be arrived at by other means. The survey chest X-ray promises to be a most valuable tool in the early detection of bronchogenic carcinoma although, needless to say, a negative report means nothing.

Bronchoscopy—It is generally agreed that histological diagnosis by bronchoscopy and biopsy is obtained in approximately 41% of primary lung carcinomas. It is doubtful, however, if it detects the carcinoma at very early stages.

Cytological Study of Bronchial Secretion—Study can be made either by examination of sputum or by means of aspiration through a bronchoscope and seems to offer great promise in histological diagnosis of primary lung cancer. It has been reported that up to 89% positive diagnosis has been made by this method.

Aspiration Biopsy—This method has, it seems, more antagonists than advocates. Many feel that there is a real danger of implantation of cancer along the needle route, and therefore this method has generally been rejected in favour of exploratory thoracotomy.

Exploratory Thoracotomy—This may be the only means of making the diagnosis in the end, and it should be undertaken without delay once the need for it is accepted. The only indication for its use may be an undiagnosed radiological opacity. Even if, upon operation, the lesion is not carcinoma, it is usually one that requires surgical removal, such as tuberculoma, hydatid cyst, actinomycosis, teratoma, chronic abscess. If inspection and palpation are not conclusive regarding the necessary extent of the resection an immediate examination of a frozen section is usually decisive.

Gross Pathology

According to Boyd, all the epithelium of the lung is derived from the lining of bronchi, and consequently all primary carcinoma of lung is really bronchial in origin. The great variability of carcinoma is due to various degrees of differentiation rather than to multiple origins.

The gross types are:—1. Hilar
2. Miliary
3. Diffuse

1. *Hilar Tumours*—These make up 80% of the cases. Their origin is from the lining epithelium of bronchi, and spread is from there into the substance of the lung. The lesion may vary from a slight roughening of the epithelium to a full-blown stenosis of the bronchus with subsequent atelectasis, bronchiectasis and abscess formation.

2. *Miliary Form*—Multiple tumours have been described under a variety of names, such as alveolar cell carcinoma. This name suggests origin from the epithelial cells lining alveoli.

3. *Diffuse Type*—This is the rarest form, and has been mistaken for lobar pneumonia at autopsy. The entire lobe or lung is converted into a solid mass of grey, firm tissue.

Microscopic Pathology

Histological studies of aspirated bronchial secretions appear to offer a means of early diagnosis of bronchogenic carcinoma, although bronchoscopic sections and thoracotomy biopsy are often necessary before a correct diagnosis can be made. The differential diagnosis must take into account such lesions in the lung as

1. Bronchial adenoma
2. Chondroma
3. Neurofibroma
4. Hamartoma
5. Cysts of lung, pleura and pericardium
6. T.B.
7. Chronic Pneumonia
8. Metastatic Tumours.

The microscopic types, according to Boyd, are three in number:

1. Adenocarcinoma
2. Squamous Cell Carcinoma
3. Small Cell type.

1. *The Adenocarcinoma*—This cylindrical cell type may be a typical adenocarcinoma or there may be no attempt at glandular formation, the cells being arranged in masses. The individual cells are tall columnar and filled with mucin as are the glandular spaces. There may be papillary projections into the lumen of the gland, or the cells may grow along the alveolar wall and may fill the alveolus completely.

An important point to remember is that these cells may be undifferentiated and there may be difficulty in distinguishing them from sarcoma.

2. *Squamous Cell Carcinoma*—These are seen as solid masses of flat squamous epithelial cells with or without cornification. It is thought that these cells have their origin in areas of metaplasia of bronchial mucosa. This type of tumour growth is usually slow-growing and often is necrotic with cavity formation. Metastases are often confined to the regional lymph nodes.

3. *Small Cell Type* (Oat cell type)—These cells are very pleomorphic, round or spindle shaped, and in the past have been mistaken for sarcoma, although the alveolar arrangement points to its carcinomatic origin.

Method of Spread

1. *Within the Lung*—The growth may spread by cells extending, or inhaled along bronchioles to form a new lining for the alveoli, or it may spread by lymphatics far and wide through the lung producing mantles of cells around distant bronchioles.

2. *Distant Spread*—The pericardium, heart and great vessels may become involved and there may be pressure symptoms referred to the trachea, oesophagus and recurrent laryngeal nerve. The mediastinal lymph nodes are always involved at some time during the course, and these lesions may so dwarf the original lung lesion that the wrong diagnosis may be made — that of sarcoma of mediastinal nodes with secondaries in the lung. Axillary, supraclavicular and cervical nodes may be involved also, and removal of one of these may clinch the diagnosis.

Distant metastases in order of the frequency of their occurrence: Liver, Bone, Brain, Kidney, Adrenal. Of the bones, the thoracic cage, ribs, sternum and vertebrae are the most frequent sufferers. Boyd points out that if a tumour of small round cells is found to involve brain, lung and adrenal and the exact origin is doubtful it is a good bet that it is primary in lung. It is suggested also that if a person in the middle age group has signs of a rapidly developing brain tumour it is likely to be a secondary and the primary should always be looked for in the lung.

Treatment

Unless treated early, bronchogenic carcinoma usually runs a rapid and lethal course. In one survey of 340 untreated patients the duration of life from the onset of symptoms to death was 9½ months. Similar series studied at the Mayo Clinic of 315 cases averaged 14½ months.

I. *Surgical Treatment*—The surgical removal of one lobe, or preferably the whole lung, is the only satisfactory means of treating lung cancer to date and one is not justified in treating the patient in any other way if he is a good surgical risk.

The incidence of operability and resectability has been increasing over the past years. Churchill reported that in 1950 cases of one series, exploratory thoracotomy was done in 40% and resections in 22% of the whole group. The increased operability may be due in part to earlier diagnosis and more radical attempts at extirpation.

The contraindications for surgery are relatively few and include patients in very poor general health, gross involvement of trachea, and evidence of distant metastases.

Survival Rate of Surgical Patients

In this series by Ariel, following surgical extirpation there was 26.5% survival for one year, and the five-year survival rate was 7.1%. Other operators claim a survival rate as high as 23.3% for five years. The drop in survival rate is rapid during the first nine months and then becomes more gradual. Thus if a patient survives the first year following resection his chances for continued survival are fairly good.

The question of palliative surgery is another controversial one. The average life of all patients subjected to surgery is 14 months from the time of operation. The average life of the patient without treatment is 9½ months. It is questionable whether the increased trauma is justified.

II. *Deep X-Ray Therapy*—Craver of the Memorial Hospital in New York reports a five-year survival rate of 3.8% of 142 persons treated with deep X-ray therapy. Other surveys have not been quite so optimistic. In the survey by Ariel of 723 patients treated with X-ray, the average duration of life from the onset of symptoms was 12¾ months. It gave a one-year survival rate following therapy of 3%, with no cures.

The following are criteria proposed for X-ray therapy:

1. *Radical Treatment* (4000-6000 R)
   (1) Operative lesions where surgery is refused
   (2) Operative lesions where surgery is contraindicated for other reasons
   (3) Lesions involving the carina or trachea
   (4) Post-operatively when small amounts of tumour tissue have been left behind because of operative difficulties
   (5) Pancoast type of tumour
2. *Palliative Treatment* (*dose determined by respiratory symptoms*)
   (1) Inoperable carcinoma with marked local symptoms
   (2) Inoperable lesions with hemoptysis
   (3) Inoperable lesions with general body weight loss, loss of appetite, malaise, fever
   (4) Metastases — where symptoms are due to extrathoracic metastases
3. *Contraindications to Primary Tissue Irradiation*
   (1) Poor general condition of the patient
   (2) Large bloody pleural effusions
   (3) Active TB in the path of the X-ray beam
   (4) Usually a previous course of irradiation

III. *Cobalt 60 Therapy.*

IV. *Radioactive Gold instilled into pleural cavity to reduce effusions.*

V. *Interstitial Irradiation*—Seeds and needles are inserted in and about the pulmonary cancer deemed inoperable at thoracotomy. There were no cure rates in one series of 17 done this way.

VI. *Nitrogen Mustard Therapy*—It may be palliative in a few cases by increasing the feeling of well being and decreasing pain and hemoptysis. Response however is transient.

From the various series of cases of bronchogenic carcinoma studied it has been shown that the average five-year survival rate is in the neighborhood of 5%. Of the various treatments which are used, the conclusion has been that surgical removal of the affected lobe or lung offers the best results.

The rising death rate from bronchogenic carcinoma has now reached such proportions as to make it a public health problem fully deserving much greater measures of control than are now being applied for its detection. It is apparent that on the basis of present knowledge routine periodical examination of the chest of men over 40 years provides the most effective means of increasing the salvage rate. Demonstration of a show by this means demands aggressive action to establish diagnoses so that early adequate treatment may effect a cure.

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Hypersensitivity

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HYPERSENSITIVITY is that aspect of immunology which deals with specific antigen-antibody relationships but attention is focused on a special consideration. In acquired resistance the antibody combines with a specific antigen and its infectivity is thwarted or its toxicity neutralized. In hypersensitive reactions, on the other hand, the concern is what happens to the tissues as a consequence of antigen-antibody reactions. The union of antigen and antibody may be revealed in a number of ways.

It is interesting that a response of the body which may be protective, i.e. the formation of antibody, may also result in injury to the tissue. The action of neutralization of antigen by antibody can go on, while independently, a hypersensitive reaction also occurs.

Terminology

The word *hypersensitivity* should be used to denote a state where there are physical manifestations as a result of antigen-antibody union in vivo. It covers that aspect of immunology which includes allergy, anaphylaxis and other variously named conditions which have the same underlying mechanisms.

Allergy was introduced by von Pirquet (1906) as a general term, denoting a condition of altered reactivity of the body. This may embrace all possible physiologic and pathologic reactions of which the body is capable and since some of these are not concerned in the hypersensitive response at all, the word is misleading. It may be used, however, to denote those clinical states where there is a specific alteration reflecting prior contact (which may or may not be evident) with an antigen.

The term *anaphylaxis* was coined by Richet in 1902 to describe the state of excessive susceptibility, the very antithesis of prophylaxis, which he was encountering in dogs undergoing intravenous injections with eel serum or extracts of sea anemones. He found that rather than becoming immune the dogs would become violently ill upon reinjection of the same material about three weeks later and often died. Anaphylaxis is now used to describe acute shock-like reactions which may occur subsequent to the injection of antigens into hypersensitive man and animals.

Types of Hypersensitive Response

There are two main categories in which most hypersensitive reactions may be placed. They are defined in terms of the true lapse between contact of the specific antigen on the sensitized host, and the appearance of visible manifestation of the reaction.

(1) Immediate reaction—urticarial type.

(2) Delayed reaction—tuberculin type. This paper will include a more extensive discussion of the immediate type of hypersensitivity with a comparison and contrasting of the delayed type later.

General Mechanisms Concerning Immediate Hypersensitivity

Although different manifestations may be evident, the immediate hypersensitive states have much in common.

(a) Rapidity of response; within seconds or minutes after contact.

(b) Relationship of reactivity to a demonstrable antibody of the blood which can transmit the hypersensitive state to a normal recipient.

(c) The non-participation of the tissues per se in the reaction with antigen, but only secondarily as a result of combination of antigen with antibody.

The following sequence of events accounts for the induction of immediate hypersensitivity and for the occurrence of an immediate type of reaction in the sensitized subject.

A. *Induction* requires a complete antigen or a hapten which combines with tissue proteins which act as a carrier. The induction period is about 10 days after primary contact. The Hypersensitive State is immunologically specific.

B. The *elicitation* of response occurs under these conditions.

(1) A sufficient quantity of antigen or hapten usually greater than sensitizing dose is required.

(2) Antigen reacts with antibody in the blood, upon cells or within cells.

(3) As a result of AG-AB reaction certain tissues are affected, and the responses result in various manifestations:

(i) smooth muscle contractions may result in pulmonary difficulties, and arterial constrictions;

(ii) injury to blood vessels may lead to leakage of fluid into tissues (edema) as well as damage to tissues supplied by occluded vessels;

(iii) degeneration of collagen with cellular infiltration and scarring may interfere with the functions of vital structures such as heart valves.

(4) The mechanisms through which these changes may be effected by the antigen-antibody reaction in vivo appear to be two:

(a) With sufficient concentration of antibody, when a large dose of antigen is injected, the resulting precipitate in itself seems to damage blood vessel walls. This may be the case in the Arthus phenomenon (later).

(b) An intermediary substance is released as a result of antigen-antibody reactions. Less antibody and antigen need be present. The chief intermediary substance released within the body appears to be *histamine* or something which acts

like it, often referred to as H-substance. Dale and Laidlaw in 1910 first pointed out that anaphylaxis shows many points in common with a syndrome produced by the injection of histamine into guinea pigs. Later this concept was associated with the general mechanics of the inflammatory response. The classical "triple response" of skin described by Lervis—erythema, central wheal and flare was noted on local injury and also on injection of histamine. The suggestion that the response to injury was caused by the release of a H-substance was also used to account for the inflammatory allergic response occurring with the injection of antigen into sensitized skin.

(Dragstedt working with anaphylaxis in dogs was able to demonstrate the presence of a histamine-like substance in the efferent blood from the liver during shock. Later it was demonstrated that the same substance was released from cells during *in vitro* antigen-antibody reactions.)

How does the union of antigen with antibody free histamine from body cells? Rappel believes that a proteolytic enzyme is activated or liberated within cells by the antigen-antibody combinations and that this enzyme in turn releases histamine which is bound to cell proteins through arginine or lycine. In humans, normal urine contains little or no histamine but moderate to enormous amounts have been found in the urine of asthmatics. Higher amounts of histamine have been found in upper respiratory tract mucous membranes and in lung tissues of allergic than of non-allergic subjects.

Substances other than histamine may be liberated during a hypersensitive reaction. A smooth muscle contracting SRS (slow reacting substance) is liberated even when reactivity to histamine has been abolished. Heparin released from the liver may account for the defect in coagulability of the blood, though a deficiency of blood platelets may occur. *Acetylcholine* may be liberated in larger than normal amounts and this may be a factor in the emotional influence on allergy. Potassium ions may also be freed into the circulation.

Types of Immediate Hypersensitivity

1. *Arthus phenomenon* — based on precipitation of antibody-antigen complex on blood vessels. With successive injections of an antigen into a rabbit at intervals of some days a moderate edema will occur at the site and remain for several hours. With further injections the edema is more pronounced and prolonged until the reaction may progress to necrosis. The pathogenic chain of events includes arteriolar spasm, endothelial damage, clumping of leucocytes to form thrombi, and exudation of fluid and blood cells into the tissues. A severe reaction may result in ischemic necrosis of the area.
2. *Evanescent Cutaneous Reactions.* — These occur in sensitized humans. They become visible within a few minutes after local injection of

antigen into the skin. They disappear early (within 3-4 hours) and never progress to necrosis. They are due to release of histamine and gives the wheal and flare response.

3. *Anaphylaxis* is regarded as the prototype of immediate hypersensitivities.

Sensitizing dose of antigen may be very small but the shocking dose must be adequate. The manifestations depend partly on the species of animal involved.

(1) *Guinea pig* — Shock is made evident in respiratory signs. Within seconds after the i.v. injection of the "shock dose" of antigen, the animal becomes dyspneic. Dyspnea is considered to be caused by contraction of smooth muscle about the terminal bronchioles, but there is also peribronchial edema. Other effects of smooth muscle contraction are evidenced by erection of hairs, incontinency of bowel and bladder. The blood pressure rises, then falls. Examination of the blood frequently discloses a lessened coagulability, leucopenia and thrombocytopenia. Death from respiratory failure may come from within 2-5 minutes. Necropsy will show the lungs expanded to the limits of the thoracic cavity.

The shock may be protracted if antigen is administered by a route other than intravenously.

(2) *Rabbit* — Here the mechanism for shock is different, and consists of contraction of the musculature of pulmonary arterioles leading to acute cardiac dilatation and failure.

(3) *Dog* — not so readily sensitized as the guinea pig. The syndrome usually resembles traumatic shock with restlessness, vomiting, diarrhoea and collapse. The dog's liver releases histamine and this affects other tissues. Death may largely be due to increased capillary permeability throughout the body with loss of fluids from the circulation. Instances of rapid anaphylactic death with a predominance of respiratory signs may also be accounted for by the large quantities of histamine released, acting upon the pulmonary musculature.

(4) *Human beings* — Acute anaphylactic shock in humans resembles most often the guinea pig type of shock. Fortunately the incidence is very low (0.1% of individuals receiving injections of horse serum). In man there is also a fall in blood pressure and temperature, with decreased blood coagulability and eosinophilia. Shock may occur in an individual in whom sensitization has been induced by previous injections of antigen (e.g. therapeutic serum) or in those in whom sensitization has been spontaneously acquired. People who are spontaneously sensitive to horse dander, for example, may be unusually liable to the production of shock by an injection of horse serum. This may follow from the minute quantity employed for intradermal testing (Case History C.M.A.J. 1951).

Case: W. J. Copeman, *C.M.A.J.*, November, 1951, page 471

Boy, age 11 — fish hook in hand. The doctor inquired if patient had

asthma, eczema, hay fever, or other allergy, with negative reply. In course of treatment, he was given skin test dose of ATS 0.1 cc. intracutaneously in the anterior aspect of the right forearm.

Two minutes following skin test the patient commenced to rub his eyes, and a copious nasal discharge appeared. He rapidly became red in the face and dyspneic. He complained of burning in his chest. A severe cough and sneeze developed which was almost continuous. In less than 5 minutes the eyes were closed due to edema of the lids, and large urticarial welts had appeared on his forearms, chest and head. There was now a large area of reaction over 2 inches in diameter surrounding the site of the intracutaneous test. The pulse was 130. The patient was acutely ill.

Following 0.2 cc. of 1/1000 solution of adrenalin chloride hypodermically, there was a subsidence of the symptoms. Two more doses of adrenalin were given at 12 hour intervals. The patient was discharged home from hospital on the second day, but some edema of the lids persisted for several days:

A negative history of allergy cannot be entirely relied upon. Adrenalin relieved the reaction.

4. *Serum Sickness* — in over ½ previously normal human beings who receive horse or rabbit antiserum for prophylactic or therapeutic purposes. Symptoms of hives, angioedema, painful joints, lymphadenopathy and fever, coming on 8-10 days after initial administration of the antigen, and persisting for several days. The interval denotes the time for antibody production and sensitization and at the end of the period (8-10 days) antigen still persists and as a result reactions occur.

   Serum sickness is imperfectly understood in several respects. It occurs often after injection of foreign serum, but less frequently following other substances with good antigenic properties, e.g. toxoids. This may be due to the quantitative differences in administered dose, but not entirely so for even with horse sera it has been noted repeatedly that some samples are more apt to induce the syndrome than others.

5. *Atopic Sensitivity*

   Atopy — out of place or strangeness. They are hypersensitive states considered to be hereditable and to be limited in occurrence to the human being. They are loosely referred to as *allergies.*

   Chief manifestations of atopic sensitivity include — asthma, hay fever, urticaria, angioedema, and probably infantile eczema. The substances most frequently responsible for clinically manifest sensitivities are pollens, feathers, animal danders, dust, milk and wheat — inhalants and ingestants. However, asthma may be caused by such a simple chemical substance as aspirin on the one hand and by infestation with worms on the other.

   These conditions are fairly familiar so I will not review their clinical pictures in the limited time available.

Characteristics of Atopic Sensitivity

1. Sensitization usually occurs spontaneously as a result of exposure to environmental agents.

2. The spontaneous occurrence is almost entirely limited to man.
3. The hypersensitivity cannot usually be reproduced by artificial (injection) methods.
4. There is an hereditary disposition to sensitization by environmental agents. About 10% of human beings are affected.
5. The antibody associated with this response (reagin) is limited to a globulin of poor combining activity for antigen, distinctive physiochemical properties and ability to convey sensitivity to cutaneous and mucosal tissues only.

Desensitization cannot be so regularly accomplished as in the case of Arthus and anaphylactic sensitivity. Circulating atopic antibody is not diminished by repeated injections of responsible antigen, but clinical improvement may occur in the face of this fact. A possible explanation of the desensitizing process is that a second type of antibody is produced on injection of the antigen which exhibits a greater combining activity for the antigen but lacks ability to sensitize normal skin. This may be called a blocking or inhibiting antibody which blocks antigen from combining with sensitizing antibodies in the tissues.

Other hypersensitive syndromes

Many diseases of unknown etiology have been attributed to a hypersensitive basis without reasonable evidence. However, in the past few years such evidence has been disclosed for a few conditions. These diseases share the basic fact that they reflect injuries to vascular tissue and collagen although they are different as categorized by clinical signs and symptoms.

Periarteritis nodosa—This disease is characterized by an inflammatory affect of the small arteries, in which the lesions progress from proliferation of the intima and inflammation of periarterial tissues to occlusion by proliferation or thrombosis. Nodules containing polymorphonuclear cells and eosinophils form on the adventitia. Symptoms may be manifold depending on the location of the most extensive arteriolar damage.

The lesions may be the eventual result of the formation of wheals in the arteriolar walls about the vasa vasorum.

The disease presumably represents the eventual pathologic change resulting from repeated or continuous immunologic responses which are of immediate type and which involve vessels following contact of antibody with antigen. Periarteritis nodosa may result from a variety of antigenic factors in the individual who presents the proper soil for its occurrence whatever that may be.

Rheumatic fever—Lesions seen in heart and other tissues as a result of an attack of rheumatic fever are related to the lesions of periarteritis nodosa. The Aschoff bodies are focal areas of degenerated collagen in the myocardium and endocardium with collections of mononuclear and multinuclear cells. Large nodules of similar histologic picture may appear

in joint capsules or the subcutaneous tissues. Similar changes have been noted in animals with induced sensitivities. Such lesions occurring in humans sensitized with horse serum and egg albumin have been described. The occasional occurrence of periarteritis nodosa complicating rheumatic fever has been observed.

The eventual etiologic factor in rheumatic fever may be more restricted. It has been suspected that the hemolytic streptococcus is related to the disease because the onset of rheumatic fever has been so frequently observed to follow respiratory infection with this organism. However, allergic responses to different antigens may take the same form. Nonetheless, strong evidence points towards the streptococcus.

Rantz and others during the war showed that electrocardiographic evidence of heart damage could become apparent shortly after the onset of an attack of acute streptococcal disease in the face of little or no clinical signs of rheumatic fever. In some instances subsequent attacks of streptococcal infection were accompanied by more pronounced changes until overt rheumatic fever was noted. Here, it was interesting that the immunologic types of streptococcus causing the succeeding respiratory infections frequently differ. The possibility exists that the responsible antigen is not a part of the streptococcus itself at all, but rather a component of the host's own tissue so altered by the activity of the organism as to become autoantigenic.

Murphy and Swift in 1949 strengthened the aspect of the relationship of streptococci to rheumatic fever by ingenious experiments with rabbits. Multiple reinjections into the skin with organisms of different type specificity evaded the factor of acquired immunity, and a series of infections could be established — a situation presumably analogous to that in spontaneous infections in humans. After sustaining 2 to 10 such injections over a period of 3 to 20 months, some of the animals became ill and developed elevated erythrocyte sedimentation rates, leucocytosis, loss of appetite and weight, post-exertional dyspnea and in some instances, cardiac arhythmia. In the hearts of these animals lesions were found in the endo-, myo- and epicardium; these containing no demonstrable bacteria and in appearance they were strikingly similar to the lesions of rheumatic fever of the human being.

Relationship of Eosinophils to Immediate Hypersensitive Reactions

It is well known that eosinophils may occur about the local sites of reaction or may be increased in numbers in the blood stream in many hypersensitive reactions. In fact their occurrence is so commonly related to hypersensitive reactions of the immediate type that their presence in abnormal numbers in any disease of unknown etiology (e.g. Hodgkins' disease) makes the factor of allergy suspect. Cortisone which modifies the hypersensitive reaction causes also a decrease of circulating eosinophils in the blood. So far all the information about these cells is observational. There is no sound idea as to why they appear or what they do.

Therapeutic Agents in Relation to the Mechanisms Concerned in the Immediate Hypersensitive States

The therapeutic measures employed in the hypersensitive states have been based upon rationales intimately related to the fundamental viewpoints of the mechanisms described. One may consider the hypersensitive states and reactions from the initial entry of antigens into the tissues, through the antigen antibody union to the final action of H-substance upon the susceptible types of tissue.

The therapeutic measures will be considered as they fit into the scheme as we now know it.

I. *Agents affecting production of antibody*

1. *Nitrogen mustard* is toxic for lymphocytes and has been found to suppress antibody formation as well as acquired resistance. However, this may be coincidental since nitrogen mustard affects various enzymic and metabolic processes as well.

2. *ACTH and Cortisone* are known to dramatically alleviate the clinical courses of rheumatoid arthritis and lupus erythematosis and have stimulated tremendous enthusiasm in those interested in diseases of hypersensitive origin. In other clinical states, beneficial effects have been described in asthma, hay fever, urticaria, dermatitis, angioedema, serum sickness and gastrointestinal allergy.

These substances do not significantly affect antibody production, but there is a prompt influence in established human hypersensitivity. The benefits here seem to be due to the inhibition of inflammation or to some of the physiologic actions, rather than interference with an immunologic process. The effects of these hormones are multiple and no definite conclusions can be reached at this time.

II. *Agents affecting antibody itself*

Desensitization has already been mentioned. Antigens used in repeated injections may combine with antibody, thus removing the agent of sensitization, or by causing an excess of circulating antibodies which may prevent the combination of antigen with antibodies on or in the cells.

III. *Agents affecting antigen-antibody combinations*

Salicylates are used in the treatment of rheumatic fever and are said to have some favorable influence upon the course of serum sickness.

These drugs *may* inhibit the combination of antigen with antibody. However, the effects on hypersensitivity may depend on the indirect influence of these drugs based on other pharmacological actions.

IV. *Agents affecting histamine*

1. *Histaminase* was demonstrated by Best and McHenry in 1930 as an enzyme existing in tissues which is active upon histamine in a test tube. However, there is no evidence that it does the same in the body and is without value in clinical and experimental hypersensitivities.

2. *Histamine azoprotein* was used in trials in the attempt that antibodies could be produced against the histamine hapten. It was hoped that these antibodies might be available to act upon the intermediary substance released by other antigen-antibody reactions. Some success was found in protection of guinea pigs against anaphylaxis but this did not apply to trials with human subjects.

(A substance called *d-catechin* has been shown to inhibit shock in 14 sensitized guinea pigs. The mechanism is thought to be in preventing the formation of histamine by inhibiting the histidine decarboxylase of the tissues.)

V. *Agents affecting histamine action on shock tissues*

1. *Sympathomimetic drugs.* Adrenalin causes bronchial relaxation and blood vessel constriction and its effects are directly opposed to those of histamine. Thus adrenalin is used to protect the body from shock or to ameliorate an attack of asthma or urticaria. Ephedrine has similar activities to a milder degree. Aminophylline acts directly on smooth muscle and is used in the relief of asthmatic attacks.

2. *Antihistaminic drugs.* These substances have contributed more than any other class of compounds to an understanding of the mediation of certain of the immediate hypersensitive reactions. The data now suggests that these agents block histamine by competing for the same receptor sites on sensitized cells. However, the drugs are not specific histamine antagonists since they do not suppress all the effects of histamine in the body. The stimulation of gastric juice by histamine is uninfluenced by most of these drugs. Also, these drugs do not affect all hypersensitive manifestations equally. In humans these substances are quite effective against the skin manifestations of serum sickness, and in hay fever, urticaria and angioedema to the extent of perhaps 80% of instances treated. However, allergic asthma responds very poorly to these drugs. One may wonder if some of their effects are based on pharmacological activities other than their antihistaminic property.

Delayed Hypersensitivities

Differences between the delayed and the immediate hypersensitivities may be outlined as follows:

I. *Induction*
- (a) *Infectious agents* require presence in the tissues either of the organism or of certain derivatives of it in addition to the responsible antigen alone.
- (b) *Chemical substances* — sensitization mediated through the skin.

II. *Nature of reactivity*
1. Longer period intervenes between contact with antigen and onset of local or systemic effects. Response is progressive — reaches its peak from 24-72 hours and may persist for several days.
2. No humoral antibody can be demonstrated by passive transfer to normal recipients.

3. There are no specific shock tissues in the nature of smooth muscle, blood vessels or collagen. Cells of the body generally are subject to injury by exposure to antigen. In some instances a particular tissue may respond.

Similarities to immediate hypersensitivities are:

1. An antigenic stimulus is necessary for induction.
2. Reaction occurs only on exposure to specific antigen.
3. Induction period of 1 week-10 days for establishment.
4. Desensitization can be effected.

Delayed Hypersensitivity in Infectious Processes

Tuberculosis is pre-eminent. A sensitive state easily demonstrable by a skin test and tissue injury and destruction which ensues from this reactivity plays a considerable part in the pathogenesis of the disease. Other diseases — brucellosis, typhoid fever, tularemia glanders, chanceroid and whooping cough. Probably a study of any bacterial infection would disclose a very general existence of this type of hypersensitive response.

Mechanisms in Delayed Hypersensitivities

Induction of delayed hypersensitivity in the case of tubercle bacillus requires, in addition to an antigen of this organism, another non-antigenic component of lipoidal nature which determines this type of hypersensitive response. The same lipid effective in determining delayed infectious allergy can also provoke the occurrence of contact sensitivity to simple chemical substances following parenteral injection. This suggests that the requirement that spontaneous contact sensitization be mediated through the skin is by reason of the skin supplying lipid of similar biological activity to that obtained from tubercle bacillus.

The intrinsic factors in the body which determine that this set of mechanisms comes into play rather than, or in addition to, those concerned with immediate hypersensitivity are not fully appreciated.

Psychosomatic Aspects of Allergy

In a survey of 50 cases of bronchial asthma, McDermott and Cobb noted that 37 patients gave a history of emotional factors associated with relapses of their disease. Other authors have remarked that although allergic substances (antigens) may represent an increased stimulus for an attack, the psychic attitude can prevent, inhibit or favor an attack.

Hansen described the case of a woman who was dining with a male friend at a rendezvous, and was surprised by her husband appearing on the scene. The results were terror and generalized urticaria. This situation involved a conditioning for the patient who was eating lobster when surprised. She always suffered from urticaria after eating lobster subsequently though never had before.

The present day belief is that most cases of asthma are doubly determined, i.e. in a person with an allergic predisposition, psychic factors mobilize the latent factors of the disease and make it apparent.

The type of psychological behaviour associated with asthmatic attacks has helped to understand the association as being mediated through autonomic nervous and chemical mechanisms. Anything that increases "vagal or parasympathetic tone" may be associated with an asthmatic attack, whereas anything that increases sympathetic tone will inhibit or benefit attacks. For instance sudden emotional outbursts as in sudden fear or rage have aborted asthmatic attacks presumably by the mobilization of adrenalin in the body.

There is a close physiological resemblance between the asthmatic attack and sexual orgasm. Both are parasympathetic explosions. It is fascinating to speculate whether perhaps the asthmatic who wheezes in a sexual situation has transposed his sexual response from genitals to lung.

Funkenstein and others have noted the low incidence of asthma among patients in mental hospitals. Also, an asthmatic who develops a psychosis is often free from asthma during mental illness, only to have the allergic attacks recur when the mental illness clears. One patient developed anxiety attacks during asthma-free periods. He returned to the clinic not because he suffered from asthma but because he wanted to have it back. He had lost his asthma after Coué (autosuggestion) treatment elsewhere but preferred it to the severe anxiety attacks which had taken its place.

Patients with mental illness and a history of asthma revealed a marked shift in their autonomic patterns during psychoses and freedom from asthma, as compared to their non-psychotic phases when they were having asthma. During the asthmatic phase mecholyl (parasympathetic stimulant) precipitated a severe asthmatic attack which persisted. During the mental illness the effect of mecholyl was less evident and quickly overcome.

An overactive sympathetic nervous function may account for the absence of urticaria in anxiety neurosis.

The question of causality as related to the primary psychological or physiological factors may come to the mind of many. When the psychological picture changed, the physiological picture changed and vice versa. It is felt that the psychological and physiological changes are two aspects of the patient's reaction to stress. For instance, cases of asthma have been arrested by electroshock treatment, the established therapy for endogenous depression. Of course, they are also successfully arrested with ACTH and Cortisone, and it may be that ECT is effective through a pituitary-adrenal mechanism.

Maude Abbott

Canadian Pathologist

Lillian M. Beattie, '54

ON March the eighteenth, 1869, Maude Elizabeth Seymour Abbott was born in St. Andrews East, a small Quebec village on the north shore of the Ottawa River. She was the daughter of the Reverend Jeremiah Babin and his wife, the former Elizabeth Abbott. Maude's father left home before she was born and her mother died of pulmonary tuberculosis seven months after her daughter's birth. As a result, Maude and her sister Alice were adopted and brought up by their grandmother, Mrs. William Abbott, whose cheerful nature, despite great personal sorrows, gave the girls a happy home.

Always thirsty for knowledge, Maude received her early education from a governess. At fifteen, she began making entries in her diaries which show an increasing desire to go to school with other girls. That same year she was sent to Misses Symmers and Smith's private school in Montreal and having spent only a year there, she won a scholarship for McGill. Here she was president until her final year of the third class of women to graduate in Arts from McGill. The women were in the Donalda Department of McGill at that time. Maude was valedictorian of her class. During her second year in Arts one of her best friends, who later became Mrs. C. H. Eastlake, a well-known artist, suggested that she study Medicine. At that time all Maude cared about was that she might continue studying at her beloved McGill. The intense love and loyalty which she had for McGill throughout her life was undoubtedly strengthened by the fact that her grandfather and great-uncle had both been present at the first meeting of the Board of Governors in 1829.

Despite her strong desire to go to McGill and a much-publicized debate, Maude along with other women was denied entrance to the Medical School. The question of co-education in medicine was strongly debated. Even Sir William Osler wrote from Pennsylvania, to oppose the expense of separate classes for women, but to support the unpopular idea of mixed classes. When McGill stood firm, its rival Bishop's College let Maude know that they planned to take women in their next classes. Through the shrewd advice of another woman medical student, she was one of the last women to obtain permission to use the wards of Montreal General Hospital for clinical study. During this time she was very lonely and rather unpopular as a student. The other students resented her unusual zeal for learning. "Maude had little to offset this. She had no special charm of manner, and with strangers was apt to be shy and awkward." In 1894, she graduated with high honors.

Immediately after graduation she went to Europe for three years of post graduate study under some of the most clever medical men of that time. Although she intended to limit her practice mainly to obstetrics and gynecology after return to Canada, her studies in Europe were not narrow. In Zurich she studied pathology and neuropathology as well as gynecology. In Vienna, internal medicine and obstetrics were studied as well as gynecology, pathology and neuropathology. Her taste for pathology and research was greatly stimulated during this time. At Edinburgh she obtained the triple qualification with the degree L.R.C.P. and S. In 1897 she returned to Montreal.

Although Maude Abbott made an attempt at private practice, she seems to have had as her goal in medicine a place on the staff of the McGill Medical Faculty. After only a few weeks of practice she became interested in a case of hemochromatosis with pigmentation-cirrhosis of the liver as reported by two of the McGill men. When Dr. C. F. Martin invited her to work at Royal Victoria Hospital, she gladly accepted and began work under the direction of Dr. Adami. Her first assignments were a statistical study of functional heart murmurs for Dr. Martin and pathological and biochemical research into pigmentation-cirrhosis for Professor Adami. The first paper, "On Heart Murmurs", based on four hundred and sixty-six cases was read at the Montreal Medico-Chirurgical Society in November 1898, by Dr. James Stewart since no women were allowed at these meetings. The result was that just four years after her graduation the Society with only one dissenting vote, passed a resolution that women be admitted to its membership.

The second paper, "Pigmentation-Cirrhosis of the Liver in a case of Haemochromatosis" was the first case to be reported in English literature. It was presented by Sir Humphrey Rolleston before the Pathological Society of London in January 1900, and was subsequently published in its "Transactions". It was the first paper ever prepared by a woman to be presented before this society.

As well as preparing these two papers Maude was at this time beginning what was to be one of the most important aspects of her life work. In 1898, she was appointed assistant curator of McGill Medical Museum and in 1900, full curator. The material in the museum seems to have been lacking in organization or labelling. Dr. Abbott had seen well organized museums in Europe and early hinted that she would like to improve the McGill system. While working in the museum, she discovered a trilocate heart which had been donated to the museum by Dr. Andrew Holmes the year the medical school was founded. In 1901 she published a paper on this congenital heart which at least until recently, was unique in medical literature. The historical research which she did while preparing this paper resulted in her being asked by the faculty to write its history for the opening of the new Medical Building in 1902. This she did after much research in the Dominion Archives at

Ottawa and other sources of information. Her work is still regarded as the fundamental source book for the early history of McGill's medical faculty.

The task of organizing the museum was complicated by the fact that no medical museum in North America was well organized. At the suggestion of Dr. Wyatt Johnson, the Dewey system of library organization was applied to the museum. Maude Abbott set about her task with enthusiasm and labelled and catalogued as many of the specimens as she could recognize. Among these were one hundred and eighty from Osler's contributions to the museum. When Osler visited the museum in 1904, there were eighty-three specimens from his collections which had no history or labels and had been set aside in the hope that even although twenty years had elapsed, he might be able to recall some of them. His memory was, as usual, adequate for the task and he was well pleased that Maude was taking such a loving interest in the museum. From the reorganization and correct labelling of the specimens, she went on to produce the "Osler Catalogue" which not only contained a classified arrangement of the specimens but also an introduction to each section which gave it the value of a brief textbook of pathology. It is fortunate that this work was pushed rather hard. By 1907, it was completed. This was also the year in which fire destroyed most of the Medical School. The museum was wrecked, but the fire did not reach the part where the Osler collection was. The next morning the specimens were carefully sorted out from the broken glass and ashes on the floor of the basement below where they had fallen through holes in the floor. Over two-thirds of the Osler collection was salvaged including the trilocate "Holmes heart". The manuscripts for the catalogue were safe and thus this work did not have to be repeated.

The students soon became interested in the museum and spontaneously formed the habit of coming in, often at 8 o'clock in the morning to hear Maude describe the specimens. In the McGill Medical Journal published after death, one of the students wrote as follows about this work: "Dr. Abbott's museum teaching started very informally as voluntary demonstrations of interesting specimens in her care; but for three successive years the senior class thought these demonstrations so helpful that they presented her with a purse in acknowledgment of their indebtedness. The appointment to a lectureship in pathology (in 1912) came on the strength of the student response to those demonstrations, whereupon they were made a part of the curriculum. As Dr. Adam Miller (late Dean of Long Island College of Medicine) has remarked, "To see a medical museum with Maude Abbott is to have every specimen live!"

In 1910, McGill, the medical college which had so firmly resisted her enrolment as a student twenty years before granted her the degree of M.D. *honoris causa.* With the onset of the first World War, Dr. Abbott longed to go overseas in one of the services, but this was denied her.

In 1919, however, the government appointed her Acting Curator of the Canadian Army Medical Museum and Managing Editor of its Catalogue. Both the collection of specimens and the catalogue manuscripts were placed in Montreal under her care. In 1923, Dr. Abbott was appointed an assistant professor of medical research. That same year she was granted a leave of absence to accept the Chair of Pathology and Bacteriology at Woman's Medical College of Pennsylvania at Philadelphia. Here she reorganized the museum and did much to encourage the medical women whom she came to know. Despite the high regard in which she was held by the students and other staff members, Maude's true loyalties remained with McGill and in 1925 she returned there.

During her absence, the Museum Department had been reorganized. Her medical research and other work to be described later resulted in the transfer of the Pathological Museum from Maude's care to Professor Oertel. Maude felt the loss of the control of the museum quite keenly, but her disappointment was somewhat relieved by her appointment in 1932 to be Curator of the Medical Historical Museum of McGill. Her work in the Pathological Museum alone would probably have made her long remembered by the people at McGill, but, as we shall soon see, this was only a part of her contribution to the field of Medicine.

Dr. Abbott's interest in museums was not limited to the one at McGill. Shortly after she went to McGill she was sent to visit several American museums. At this time, she suggested an International Society, but no one seemed enthusiastic. In 1907, shortly after the fire, she enlisted the support of Major Carroll of the Army Medical Museum, Washington, D.C., and the International Association of Medical Museums came into existence. The purpose was to have the leading museums in North America and Europe as members. Maude was the first secretary-treasurer and editor of the "Bulletin" which was published. She held the former position until her death, and was editor until 1938. After her death, Dr. William Boyd, writing in the McGill Medical Journal, said, "A meeting of the association without 'Maude' as the central point around which everything revolved would be like witnessing the play of Hamlet without the Prince of Denmark."[5] The organization, which many regard largely the result of her effort, was in 1941 still unique in the world and had nearly four hundred members.

After Sir William Osler's death December 30, 1919, Maude Abbott gained the permission of the association to publish a memorial volume in his honor. Almost all the work of this volume was done by her and it is little wonder that she was very busy in the years 1920 to 1926. The many thousands of dollars required were raised by her. She wrote individual letters to the many medical men whom Osler had encouraged to better success in medicine. These men were asked to contribute an account of their personal acquaintance with Osler. The contributions were edited by Maude Abbott until the famous "Bulletin" No. IX or

the Osler Memorial Volume was published as a book of over 600 pages. It has been said to be second only to Dr. Harvey Cushing's "Life" in biographic importance. Maude's personal contribution to it was a classified bibliography of all Osler's publications which appeared at the end of the book and was revised and reprinted as a separate volume in 1939. In this latter endeavour she was assisted by a McGill medical student, William C. Gibson, who writes of his work in the McGill Medical Journal

The work for which Maude Abbott is best known is probably her study of congenital heart disease. All the time that she was reorganizing the museum, lecturing to students and nurturing the Museum Association, she seems to have been adding to her study of hearts. In 1905, she was asked by Osler to write the section on Congenital Cardiac Disease in his new "System of Medicine." Four hundred and twelve cases with autopsy findings were treated in a statistical manner for the chapter of one hundred and three pages. In later volumes the size of the monograph was doubled. The second volume's chapter was based on six hundred and thirty-one autopsies. This was in 1915. In 1927, the last edition was published with a basis of eight hundred and fifty autopsies. Dr. Thomas McCrae edited this volume and had to wait a considerable time for her to finish the revision of this section.

Three other large monographs were published by Dr. Abbott on congenital hearts. One on "Treatment" appeared in the Forscheimes System of Therapeutics in 1924. Her second monograph on "Diagnosis of Congenital Cardiac Disease" in Blumer's "Bedside Diagnosis", published in 1928, was responsible for this book being two years late in being ready to be printed. Dr. Blumer wrote many letters, pleading with her to limit her remarks to the more common forms of congenital heart disease and those which could be diagnosed at the bedside. Part of one such letter, written in 1926 after he had received a few pages of the manuscript, is given here:

> "I see that you have *not* carried out my request to make your article short and practical. The first thing I find on page 13 is congenital rhabdomyoma. Must I again remind you that this is a work on diagnosis, and practical work, and that it is of course absolutely impossible for anybody to diagnose a congenital rhabdomyoma or any other tumour of the heart muscle during life.
>
> Please come down to earth and send me a short practical article."[7]

This last request does not seem to have been complied with, as the completed monograph was one hundred and sixty pages in length. The third large monograph was written for Nelson's Loose Leaf System on

[7]MacDermot, Op. cit. p. 150.

"Congenital Heart Disease". This was a statistical survey of one thousand cases. This manuscript, like many others, was also late in reaching the publisher.

Maude Abbott's work on congenital heart disease was not, however, confined to writing monographs. In 1931 she was invited to display an exhibit on the subject before the New York Academy of Medicine during the Graduate Fortnight in Cardiology. The arrangement of the many types of congenital heart disease with their chief clinical and pathological characteristics was based on the Clinical Classification of Cardiac Defects which she had made earlier. This classification is still used today. The next year the exhibit was made suitable for travel and was presented before the Centenary meeting of the British Medical Association in London, England. This exhibit was four feet in height and thirty-two feet long. In the British Medical Journal, the following description is found:

> The exhibit included a large and representative collection of pictures, photographs, art drawings and paintings, charts, diagrams, radiographs and tracings of various kinds. . . . It also included a series of wax reconstruction drawings, with some fifty anatomical specimens showing various types of fish and reptilian hearts and cardiac anomalies mounted on glass frames in square jars. . . . The exhibit was completed by a chart showing the statistics and special features of 1,000 cases of congenital heart disease and necropsies analyzed by Dr. Abbott.[8]

In 1935, the exhibit was shown at a joint meeting of the American and Canadian Medical Associations in Atlantic City. Here it was given honorable mention. In June, 1936, when the exhibit was displayed at the Ontario Medical Association Convention in London, Ontario, it won a gold prize.

It was felt that this exhibit was too valuable to fade into oblivion and it was suggested to Maude Abbott that its information should be incorporated in an atlas. Photographic reproduction of the whole collection of pictures and specimens as they appeared in the display was found to be unsatisfactory for technical reasons, and so much time was expended in building up the Atlas of Congenital Cardiac Disease which was published in 1936, when its author was sixty-seven years of age. This classic volume is a pictorial retrospect of the entire subject.

Following this, Dr. Abbott made plans for a textbook on congenital heart disease and in her seventieth year received a grant from the Carnegie Foundation for this ambitious undertaking. It is regrettable that a cerebral hemorrhage which she suffered in July, 1940, prevented her carrying out this plan. She did not fully recover from this episode and died on September the second, 1940.

[8]British Medical Journal, December 31, 1932.

As well as her interest in museums and hearts, Maude Abbott was keenly interested in Medical History. The history of the Medical Faculty at McGill was mentioned earlier in this paper. This was expanded later and published as a booklet entitled, "McGill's Heroic Past," during the centenary of that University. In 1930, a book on "Medicine and Surgery in the Province of Quebec", was published in a series of books about Quebec province. She also stimulated an interest in the history of the nursing profession. She lectured in this subject to the McGill Graduate School Nurses from 1921 to 1933. Her lectures about Florence Nightingale were especially well known. The two hundred slides which she had for her nursing history lectures were copied and distributed by the Teachers' College of Columbia.

The influence of Sir William Osler in Dr. Abbott's life is difficult to accurately assay. She was one of the most ardent hero-worshippers of this widely beloved physician. She first met Osler in 1898 when she was making her initial visits to American museums. She went to his "rounds" in Baltimore and quite characteristically suffered a small accident — the crushing of a finger in a swing door, just as they were leaving the ward. Osler subsequently invited her to have dinner with him that evening and sit in on his Saturday evening conference with the senior students who were acting as clinics clerks. He encouraged her to reorganize the McGill museum and later on a visit to McGill was well pleased with her work. When she wrote to Osler in 1899 about the Holmes heart, he began his long continued encouragement for her to study congenital heart disease. We have already noted that in 1905 Osler asked her to write a chapter for his new textbook. When he received her monograph, he wrote to her, "It is by far and away the very best thing ever written on the subject in English — possibly in any language."[9] "Osler neither over-estimated nor did he depreciate her capacities. He gave direction to her intensity of purpose, and took her work as seriously as it deserved. His encouragement was naturally of immeasurable solace and support. Little wonder that he was her 'hero'."[10]

In 1911, Maude had been invited during one of her European tours to spend a weekend at Oxford with Osler and Lady Osler. Upon her arrival in England, however, she developed acute phlebitis in one leg. The rather fortunate result of this misadventure was three weeks vacation at Oxford. The Osler Memorial Volume and classified bibliography were part of her tribute to her hero. In addition she gave many lectures about Osler.

Although Maude Abbott did not seek honor or prestige for herself it was inevitable that she should be highly honored by the medical profession. From 1915 until her death, she was a member of the editorial board of the Canadian Medical Association Journal and it was to no

[9]MacDermot, op. cit. p. 102.
[10]Ibid, p. 103.

small degree through her efforts that the Journal was carried on through the war years when many of its editors were overseas. In 1931, she was a charter member of the Royal College of Physicians in Canada. Four years later, she was made an honorary member of the American Association of the History of Medicine and also a fellow of the Royal Society of Medicine in London, England. 1936 was a year of sorrow and great joy for Dr. Abbott. Despite her pleas for an extension of time, of which three months was granted, she along with several other faculty members was made to retire because of the University laws for retirement. That same year, however, she was the first woman to be elected to the Osler Society at McGill and she received the degree Doctor of Laws, *honoris causa*. This degree is the highest honor which McGill could give her.

Immediately after convocation, Maude left on a trip to California where she lectured extensively and led a busy social life as well. The climax of this visit was when she gave the Stanley P. Black Foundation Lecture at Pasadena. Her subject here was, "The Influence of Sir William Osler. A Personal Reminiscence." About this time she learned that she had been given an honorary fellowship in the New York Academy of Medicine.

In 1937, Dr. Abbott became the first honorary member of the newly formed California Heart Association. Later that year she was made an honorary member of the Cardiac Society of Great Britain and Ireland.

The next year someone who preferred to remain anonymous gave ten thousand dollars to McGill University, to found the Maude E. Seymour Abbott Scholarship. The interest is used yearly as a scholarship for a worthy study in medicine, although Maude would have preferred to have it used for students who would assist her in cardiac research.

In June 1940, the month before her fatal cerebral vascular accident, she was further honored by being made a senior fellow in the Montreal Medico-Chirurgical Society and of the Canadian Medical Association.

From the large amount of work which she did, we know that Maude Abbott had great energy stores. She was always enthusiastic about starting any new project which appealed to her and although at times her ways seemed disordered to others she had an unusual grasp upon what she was doing. In the Canadian Medical Journal at the time of her death her mental powers were summed up as follows:

"Doctor Abbott's mind was characterized by three virtues, patience, perseverance, and versatility. While she often flitted from point to point in a way that was disconcerting to the mere male, yet she eventually came to order, and the final result was a piece of work, logical, coherent, and eminently worth while. Her magnetism was such that she got things done."[11]

[11]Canadian Medical Association Journal, October 1940. Vol. 43, p. 395.

She very willingly and successfully sought money and honor for her work and literature, but never for herself. Her financial status seems to have often been quite precarious. Her financial problems were increased by the mental illness which her sister Alice developed. Maude would not consent to her being hospitalized, but rather paid a woman to be her sister's companion and guardian. Many times she was called from Montreal when her sister had become excited and disturbed. Maude always left whatever she was doing and returned to St. Andrews to pacify Alice.

Dr. Abbott has been described as about five feet, six or seven inches tall and weighing two hundred pounds more or less. She always wore a black dress that had a semblance of a belt, but looked like a bag with a hole for her head and two for her arms. She wore no ornaments, rings or jewelry other than a single string of pearls.

Her students highly respected her both as a teacher and as a friend. When Dr. Abbott was at a party or other social event, there was certain to be a warm, happy atmosphere. As well as telling amusing stories, she had a way of doing things in a manner which provoked amusement both in her companions and in herself. Professor Boyd has given us quite an insight into her character when he wrote the following after her death:

"Perhaps the keynote to her character was enthusiasm, which in turn was the basis of her extraordinary energy. Whatever the subject which was engaging her attention, it did so to the exclusion of all else. This was the source of her power, although it was sometimes a source of difficulty to her friends. Once after a long day of meetings I had settled down to enjoy myself with a few intimates in the manner which men are wont to do on such occasions, when Maude appeared and carried me off to go over the proofs of her Atlas of Congenital Heart Disease. On this occasion the proofs outlasted the party! Her energy was phenomenal. I can recall a day which she spent in Winnipeg a little over three years ago. Arriving in the morning, she visited the medical school and in particular the pathological museum. She then attended a luncheon meeting at the Children's Hospital at which she examined, demonstrated and discussed half a dozen cases of congenital heart disease. A visit to the hairdresser was followed by an address to the students at the Medical School on the classification of congenital heart disease, followed immediately by a talk on the earlier period of Osler's career. The rest of the day was occupied by a dinner party, a visit to the Nurses' dance at the Hospital, and an hour's talk (standing) on returning home. As standing, even at the beginning of the day, soon tires me, I was almost moribund when she finally decided to retire for the night. All her friends familiar with her restless energy of mind and body will be glad that the end was brief.

"It would be easy to give a catalogue of Maude Abbott's objective activities; it is much more difficult to express in words the subjective qualities which went to make up her personality. Only those who were brought in contact with her warm heart, her readiness to help lame dogs over stiles, her unselfishness, her enthusiasm for everything connected with the best in medical science, her reverence for her hero, Osler, can fully appreciate the impondrable qualities which made her such a power and inspiration."[12]

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Hyperparathyroidism

W. A. D. Anderson, M.A., M.D.

Dr. Anderson, Professor of Pathology at the University of Miami School of Medicine, discusses in this article the important but often unrecognized relation between renal disease and hyperparathyroidism.

ALTHOUGH it is intended to consider particularly the relationship of the kidneys and renal disease to hyperparathyroidism, as a background a brief review of the general subject is presented.

The parathyroid glands produce a hormone concerned with the metabolism of calcium and phosphorus, and the maintenance of normal levels of these elements in the blood. Disturbances in parathyroid function may be in the direction of decreased activity (hypoparathyroidism) or increased activity (hyperparathyroidism). Hyperparathyroidism may be due to a functioning tumor (adenoma or carcinoma) of a parathyroid gland, or to hypertrophy or hyperplasia (primary or secondary) of all parathyroid tissue. It may result in excessive mobilization of calcium from bones, leading to the skeletal condition of generalized osteitis fibrosa, calcium depositions in kidneys and other soft tissues, and renal calculi.

The parathyroid glands, usually four in number, are developed from the endoderm of the 3rd and 4th branchial pouches. Usually located as upper and lower pairs posterior to the thyroid, they are occasionally embedded within thyroid tissue but separated by a connective tissue capsule. Because the anlage of one pair of parathyroid glands is in close association with the anlage of the thymus, it is not uncommon to have one or more glands in the mediastinum, near or even embedded in thymic tissue.

The parathyroid glands are brownish-yellow, oval, somewhat flattened bodies, each measuring (in the adult) about 1.5 x 3.5 x 6.5 mm., and having a total weight of about 120 mg. (4 glands).

The parenchymal cells may be arranged in solid masses or in cords or columns. Acinar or follicular structures may be found, tending to increase in frequency with age. Adipose tissue is often present interstitially, and this is replaced or decreases and disappears when there is hyperplasia or adenomatous growth.

The parenchymal cells are of 3 main types: (1) chief cells, which compose the bulk of the gland; (2) pale chief cells or water-clear cells, which have a clear, pale or vacuolated cytoplasm and a distinct cell membrane and are somewhat larger; and (3) oxyphile cells, which are

larger than chief cells, polygonal, and with acidophilic granules in the cytoplasm. The oxyphilic cells appear to increase in frequency with age, and may be degenerate forms with relatively little function.

The mechanism and point of action of the hormone have been a matter of dispute. There is good evidence that the parathyroid hormone has a direct effect on bone, stimulating resorption and raising the level of calcium in the blood. It is known also that the hormone regulates the renal excretion of phosphate. In a normal individual, administration of parathyroid hormone results in a phosphate diuresis, lowering the level of the serum phosphate, which in turn results in increased concentration of calcium in the blood and increased renal excretion of calcium. In the presence of normal renal function and a constant pH, the values for serum calcium and phosphorus tend to have a reciprocal relationship. If the value for phosphorus falls, the value for calcium rises, and vice versa. If, in hyperparathyroidism, it is impossible to obtain sufficient calcium through the intestinal tract, the calcium stores in the bones are drawn upon.

Hyperparathyroidism

Excessive parathyroid function may be due

(1) to a benign or malignant neoplasm (adenoma or carcinoma) of parathyroid tissue;
(2) rarely to primary or idiopathic benign hypertrophy and hyperplasia of water-clear cells of all the parathyroid glands; or
(3) to a diffuse hyperplasia of parathyroid tissue secondary to a disturbance of calcium and phosphorus metabolism originating elsewhere in the body, as in renal failure.

In any of these types, the excessive hormone may mobilize calcium from bones, bringing about the skeletal changes of osteitis fibrosa cystica. The blood contains an increased concentration of calcium, and in the presence of active bone decalcification, of alkaline phosphatase, but a low level of phosphorus. Increased calcium is excreted in the urine. Metastatic calcification and renal damage are the other important features of hyperparathyroidism.

Adenomas of a parathyroid may be composed of any of the three main varieties of cells found in the normal gland, but most of them are composed of chief cells. Tumors composed of oxyphilic cells may be inactive and not produce excessive hormone. Malignant tumors of the parathyroid are relative uncommon.

A few cases of primary hyperparathyroidism have been due to a diffuse hypertrophy and hyperplasia involving all the parathyroid tissue. The glands are rather uniformly composed of excessively large cells of the water-clear type. The cause is unknown.

Not all cases of hyperparathyroidism, and according to Albright, a minority, are associated with manifest osteoporotic lesions of the skeletal

system. The fully developed skeletal condition is the generalized osteitis fibrosa cystica of von Recklinghausen. It is characterized by distortion of the skeleton due to insufficient mineralization as a result of osteoclastic resorption, and by replacement of the osseous tissues and marrow spaces by fibrous tissue. In advanced cases there are giant cell tumors and cysts. Markedly involved bones are soft and easily deformed or cut. The change is essentially an osteoclastic resorption of bone and its replacement by connective tissue in which there are abortive attempts at new bone formation. When mild, the gross change in the bone is merely a slight porousness, and microscopically mild generalized osteoporosis and marrow fibrosis. In more advanced cases, large fibrous scars develop in place of the original spongy bone. Some of these areas are brown due to blood pigment and contain multi-nucleated giant cells — hence called brown or giant cell tumors. Cysts, lined by connective tissue, may result from degeneration or hemorrhage, but are not always present.

Pathognomonic roentgenographic changes in the milder cases are subperiosteal resorptions, seen particularly well in the phalanges of the hands. Demineralization of the skeleton is usually most intense in the extremities and the skull. It should be emphasized, however, that the skeletal changes are generalized, and not focal, localized or regional.

Effects of Hyperparathyroidism on the Kidney

The original observation of hyperparathyroidism having an associated skeletal disease resulted in the condition being suspected only in the presence of such disease. However, in 1905, MacCallum first drew attention to a relation to renal disturbance when he reported a tumor of a parathyroid gland with associated chronic renal disease. Following that, several scattered reports indicated the coexistence of hyperparathyroidism and disturbances of the kidney, but the true frequency and importance of a relationship to renal disease was not realized until the work of Albright and others in Boston in the 1930's. In this relationship, it is important to bear in mind that the kidneys appear to be end organs on which the parathyroid hormone acts (by lowering the renal threshold for phosphate), and that hypercalcuria is a constant and fundamental part of the disturbed metabolism in hyperparathyroidism. Hyperparathyroidism causes a reversal of the usual path of excretion of calcium from the body. In a normal person, most excreted calcium is found in the feces, but in hyperparathyroidism most of the calcium is excreted by way of the kidneys. Apparently independent of the hypercalcuria, parathyroid hormone promotes diuresis, and in acute overdosage with parathyroid hormone death may be due to dehydration and loss of electrolytes. One may wonder if there is a specific renal tubular damage which interferes with the function of tubular resorption.

There are two fundamental facts in the relationship of the kidneys and hyperparathyroidism:

(1) Hyperparathyroidism, whether arising primarily in a functioning neoplasm of parathyroid, or secondarily in response to some stimulus from elsewhere, may produce renal damage varying from slight to severe, and modified probably by other factors in addition to the severity of the hyperparathyroidism. The damaging effects on the kidneys may have at least three components which may occur in varying combinations and degrees of severity, but which are not necessarily unrelated. These three components are:

(a) a specific damaging effect of excessive parathyroid hormone on renal structures (tubules);
(b) deposition of calcium salts in renal tissue (metastatic and dystrophic calcification) and popularly termed nephrocalcinosis; and
(c) the formation of renal calculi, with its attendant renal complications, including pyelonephritis.

(2) Primary renal disease may result in parathyroid hyperplasia and hyperfunction (not just compensation), the degree and effects of which are modified in individual cases by the severity and duration of the renal deficiency, and by other factors influencing the metabolism of calcium and phosphorus.

The evidence for a specific damaging effect of excessive parathyroid hormone on renal tissue is seen both in the results of injection experiments in animals, and in some cases of acute hyperparathyroidism (parathyroid poisoning) in man. The damage to renal tissue may be entirely out of proportion to any deposition of calcium.

Renal calcification (nephrocalcinosis) is probably a fairly constant accompaniment of hyperparathyroidism if one includes all minor or microscopic degrees. In some cases of hyperparathyroidism, it is a prominent or even the outstanding feature. But it is not always the same or involving the same portions of the kidney. Perhaps it is most commonly a metastatic calcification with precipitation of calcium salts within tubules, the calcium casts causing tubular obstruction. That the deposited calcium comes from bone may be shown by radioactive calcium ($Calcium^{45}$). In a series of experiments with rats, radioactive calcium deposited in the skeleton could be mobilized by injections of parathyroid extract and the metastatic deposition in the kidney demonstrated by autoradiographs. The sites of early deposition in the kidney appear to correspond roughly to the areas of phosphatase activity in tubular lining cells, but the autoradiographs also revealed radioactive material in the cells of collecting tubules near the tips of papillae. In acute and severe hyperparathyroidism, the tubular basement membranes and walls may be most heavily calcified, and here there appears to be evidence of dystrophic calcification, the calcium precipitation being preceded by damage of the renal parenchyma. In prolonged severe chronic cases of hyperparathyroidism, the calcium deposits may appear to be mainly in

interstitial tissue and peritubular, and calcific masses of calculus proportions may be found within the renal tissue. Plugging and then destruction of tubules by calcium casts may account for some of these findings, and the eventual degree of renal damage may be severe.

The formation of renal calculi is one of the commonest manifestations of hyperparathyroidism, an observation which has been particularly emphasized by Albright. He has emphasized the practical importance of studying patients with renal lithiasis to detect those cases which have hyperparathyroidism. In Albright's experience in Boston, about 5 per cent of patients with renal stones were found to be suffering from hyperparathyroidism. Keating estimated that 2 to 4 per cent of patients with renal lithiasis seen at the Mayo Clinic have hyperparathyroidism. In most areas, the estimates probably would be slightly lower than these. The stones are commonly of calcium phosphate or calcium oxalate composition. Complications of obstruction and pyelonephritis may follow.

Renal Hyperparathyroidism

It has been established, both by experimental studies and by extensive detailed studies in cases of renal disease in man, that renal insufficiency may give rise to parathyroid hyperplasia, and commonly does so when such renal insufficiency is prolonged. There has been some question whether this was a purely compensatory change or may actually lead to pathologic effects as a result of excess hormone produced by the enlarged glands. Secondary parathyroid hyperplasia may be found in other conditions in which there is disturbance in calcium and phosphate metabolism, such as rickets, osteomalacia, multiple myeloma, metastatic skeletal carcinomatosis, etc. However, it is only in prolonged renal insufficiency that there is evidence of secondary hyperparathyroidism.

The hyperplastic glands are composed mainly of dark chief cells, are uniform throughout in their appearance, and have little or no interstitial fatty tissue. The actual stimulus to the parathyroid hyperplasia is apparently continued disturbance in the normally highly constant levels of calcium and phosphorus in the serum. It is only rarely that renal insufficiency is sufficiently prolonged and of a degree to produce clinical evidence of hyperparathyroidism. Renal lesions in which large amounts of renal parenchyma are lacking or destroyed, and which are stationary or only slowly progressive, may result in changes which are characteristic of hyperparathyroidism both roentgenographically and pathologically. In adults, this condition of renal osteitis fibrosa cystica is characterized by phosphate retention with a high serum phosphorus level, slightly high, normal or reduced serum calcium, marked acidosis, prominent metastatic calcification, often very marked in blood vessel walls, and the resorptive and fibrotic bone changes of generalized osteitis fibrosa.

In children, the skeletal changes are modified by their development before bone growth is completed and the epiphyses united, and are often included under the variety of conditions which have been labelled renal rickets or renal dwarfism. The underlying renal lesion is most commonly a developmental imperfection in the kidneys or urinary tract, such as congenital hypoplasia, congenital polycystic disease, strictures of the ureters or congenital valves of the urethra. Pyelonephritic changes are often an added factor in such cases. Some cases appear to have been due to cystine disease.

In the skeletal lesions there are other factors in addition to excessive parathyroid hormone. The persistent chronic acidosis of this condition produces skeletal effects. Retention of phosphate and its excessive excretion by the bowel, where it may combine with ingested calcium and be excreted, may result in calcium insufficiency. While the changes in the shafts of the bones are similar to those due to hyperparathyroidism in the adult, characteristic changes occur in the epiphyseal cartilages. The epiphyseal cartilages are greatly increased in bulk, show degenerative changes, defects of calcium deposition, and marked distortions. Stresses and strains cause the cartilage to be bent and twisted, and extreme deformity often results. Metastatic calcification in arteries, heart, lungs and other tissues may be a prominent feature in these cases.

BILL

There have been many changes at the Medical School since 1926. Research has displaced teaching space. Students have come and gone. Staff has changed, the old giving way to the new. Yes, even a succession of deans has risen on the horizon, flickered and were gone. But Bill Byles goes on forever.

Working in relative obscurity, Bill has earned for himself a place in the memory of those whose faces now stare from the rogues' gallery on the common room wall—a place unique and firmly entrenched.

The amiable and capable keeper of the bull-dog clamps and mosquito hemostats, the loss of which has meant the whip to more students than care to admit it, was born in Yarmouth County, Suffolk, England on July 17, 1900. He received his education in England at Beccles, a school dating back to Norman times, and for five years worked for the English Railroad in the Works Department. He met his wife in England and they were married in Beccles in 1922.

In 1926 Bill joined the staff of the Medical School as Technician under Dr. F. R. Miller. He soon became Senior Technician, the position which he holds today.

A keen observer of the passing parade, Bill recalls a wealth of anecdotes and experiences relating to the deans under whom he has worked, and to various staff members, to say nothing of the antics and foibles of the student body.

In particular, Bill feels that the student body is not what it used to be. In general, they are not as wild as in years past. Memories of the now defunct Annual Barbecue bring a smile that is perhaps best not elaborated on. For details I suggest you call on the 1926 - 1938 Alumni.

Bill recalls vividly the deans that guided the destiny of the Medical School since 1926. He remembers with respect and admiration the late Dr. McKibben, whose ways with the staff and student body were always those of a man sincerely interested in their welfare.

It is fitting to call attention to the energy and real interest with which Bill has always carried out his duties. Full many a student whose bungling hands have fouled up a muscle-nerve preparation has been saved by the timely arrival of Bill's capable fingers. Having trouble cannulating that frog's artery? Guess who you call. Kymograph not working? You want a clamp? Probe? Anything? Name it, and nine will get you ten that Bill has it.

Bill is kept busy from 8 in the morning until the work is done at night, the time being anywhere from 5 to 10 p.m. Labs must be set up, demonstrations prepared and set up, research projects cared for, animals tended and equipment prepared. But despite his many trying experiences at the hands of the students, Bill still enjoys his work. Bill Byles is our choice for the most popular man in the Medical School.

Books in Review:

THE PHYSIOPATHOLOGY OF CANCER

F. Homburger, M.D. and William H. Fishman, Ph.D., 1031 pages and illustrations. Published by Paul B. Hoeber, New York. Price $23.00.

This volume is best adapted to the uses of persons engaged in basic research in cancer. The predominant theme is experimental as opposed to clinical. In the first part of the book the emphasis is laid on the biology of cancer as experimentally produced and studied in various laboratory animals. This gives the reader a basic picture of cancer as a biological entity. In this section, the genetic, nutritional, viral and hormonal factors are separately discussed with a large number of references to the literature.

In the second part, there are a series of thorough discussions on the physical and chemical problems involved. The effects of radiation and the chemical significance of the nucleic acids are particularly well handled.

The last 350 pages of the book deal with clinical investigations and practical applications. Under the latter heading are applied exfoliative cytology, radiation therapy, diagnostic tests and chemotherapy.

Thus it may be seen that well over half the book is concerned with the basic observations gleaned from experimental studies in the laboratory. It is always useful for the beginner in any field to have a large list of references from which to commence his own work. In this book there are around 4367 references covering all aspects of the work done on cancer. This list covers the salient features of work done up to late 1952.

—JAMES F. WHITFIELD, B.Sc., M.Sc.